

## Incidence and Risk Factors of Retinopathy of Prematurity among Preterm Infants in Shiraz/Iran

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### Abstract

**Objective:** Retinopathy of prematurity (ROP) is a serious complication in preterm infants. To avoid this complication the risk factors leading to the disabling disease should be evaluated and prevented.

**Methods:** This is a descriptive study. All preterm infants with birth weight under 1500 g and preterm infants with birth weight between 1500-2000 g who had unstable clinical condition and admitted in neonatal intensive care unit from February 2006-March 2007 at tertiary hospitals of Shiraz University, Iran, were introduced into the study. All infants are examined by indirect ophthalmoscopy. Risk factors analysis was performed in two groups. Group 1 consisted of infants with no ROP or ROP that regressed spontaneously, and Group 2 of those with severe ROP that needed laser therapy.

**Findings:** Of 199 preterms, ROP that needed laser therapy was detected in 19 (9.5%); 65 (32.6%) had ROP that regressed spontaneously and 115 (57.8%) had no ROP. Risk factor analysis showed significant *P*-values for gestational age, birth weight, Apgar score of first minute, mean duration of mechanical ventilation, mean duration of oxygen therapy, eclampsia-preeclampsia, hypoxia, hyperoxia,  $P_a\text{CO}_2 > 60$  mmHg,  $\text{pH} > 7.45$  and frequent blood transfusions. Using stepwise logistic forward regression showed the three factors mean duration of oxygen therapy, birth weight and mechanical ventilation to be independently significant variables for increasing the rate of ROP.

**Conclusion:** The main risk factors for development of threshold ROP are low birth weight, mechanical ventilation and duration of oxygen therapy. So it seems that prevention of premature delivery and judicious oxygen therapy is the main step for prophylaxis of ROP.

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**Key Words:** Retinopathy of prematurity; Incidence; Risk factors; Treatment; Hyperoxia

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## Introduction

Retinopathy of prematurity (ROP) is characterized by abnormal vascular development of retina in premature infants<sup>[1]</sup>. It is the main cause of visual impairment in premature infants<sup>[2]</sup>. It has been believed for many years that oxygen therapy increases the risk of ROP in preterm infants<sup>[3]</sup>. However, ROP can occur even with careful control of oxygen therapy<sup>[4]</sup>. Several factors increase the risk of ROP, especially those associated with short gestational age and low birth weight. Moreover, after oxygen therapy not all preterm infants develop ROP<sup>[5]</sup>. To investigate the significance of possible risk factors, we collected data in all preterm infants with birth weight under 1500 gm and preterm infants who had unstable clinical condition with birth weight 1500-2000gm.

## Subjects and Methods

The objective of this study was to determine the incidence of ROP and evaluate possible risk factors associated with the development of severe ROP that needed treatment in all preterm infants with birth weight under 1500 gm, and all preterm infants between 1500-2000 gm but had unstable clinical condition who had been hospitalized in the neonatal intensive care unit at Shiraz tertiary hospitals, Iran, from February 2006 to March 2007 and survived. Preterm neonates who did not appear to follow up examinations are excluded from the study. Sampling was by simple method. The study was approved by ethical committee of Shiraz University of Medical Sciences and informed consent was obtained from the parents.

Gestational age was determined by either the last menstrual period or ultrasound at first trimester of pregnancy and confirmed by physical examination of the neonate. A single ophthalmologist did all eye examinations.

Indirect ophthalmoscopy was performed by 28 diopter lens. Mydriatic eye drop was instilled 30 minutes before examination. Timing of first

eye examination, follow-up examination and initiation of treatment was according to guidelines of American Academy of Pediatrics for screening examination of premature infants for retinopathy of prematurity published at 2006<sup>[6]</sup>(Table 1).

**Table 1:** Timing of first eye examination based on gestational age at birth

Gestational age at birth (weeks)	Age at initial examination(weeks)	
	Post menstrual	Chronologic
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

Follow-up examinations were recommended by ophthalmologist according to the international classification of ROP recommendations<sup>[7]</sup>. All infants were scored clinically using Ballard scores.

An infant was classified as small for gestational age if the birth weight for gestational age (GA) was below the 10<sup>th</sup> percentile, using updated Bobson and Benda's chart<sup>[8]</sup>.

Intraventricular hemorrhage was diagnosed by serial cranial ultrasound studies.

PaO<sub>2</sub> and PaCO<sub>2</sub> and pH were determined in arterial blood. Hyperoxia was accepted when PaO<sub>2</sub>>100 mmHg, hypoxia by PaO<sub>2</sub><50mmHg, acidosis by pH<7.20 and alkalosis by pH>7.45. Oxygen therapy was applied according to the patient's clinical condition and arterial blood gas criteria with mechanical ventilation – CPAP mode – or hood without blender.

Statistical analysis was performed by using the statistical package for social sciences (SPSS) program. Univariate comparison of risk factors between groups without ROP, ROP not requiring treatment or ROP regressed spontaneously and ROP requiring laser therapy were evaluated

**Table 2:** Mean and standard deviation for birth weight and gestational age in groups of premature infants screened for retinopathy of prematurity

Groups of premature infants		Gestational age (weeks)	Birth weight (gm)
<b>No ROP (N=115)</b>	Mean (SD)	31.5 (1.9)	1517.9 (285.8)
	Range	26-35	800-1999
<b>ROP that regressed spontaneously (N=65)</b>	Mean (SD)	30.2 (1.9)	1244.6 (294.4)
	Range	25-36	600-980
<b>ROP that needed laser therapy (N=19)</b>	Mean (SD)	29.0 (2.3)	1145.8 (329.3)
	Range	26-32	700-1900
<b>Total (N=199)</b>	Mean (SD)	30.8 (2.1)	1393.1 (327.2)
	Range	25-36	600-1999

\* ROP: Retinopathy of prematurity

using Student's t-test, chi-square, variance analysis with appropriate significance of  $P < 0.05$ .

Stepwise logistic forward regression was used to evaluate factors predictive of development of ROP.

## Findings

One hundred and ninety nine infants were evaluated from February 2006 to March 2007 consisting of 93 (47%) girls and 106 (53%) boys. 115/199 (57.8%) were without ROP, 65/199 (32.6%) had ROP that regressed spontaneously

and needed no treatment, 19/199 (9.5%) had severe ROP that needed laser therapy. In the group with laser therapy the minimum of GA was 26 weeks and maximum 32 weeks, the mean GA was  $29 \pm 2.35$  weeks.

In the group with laser therapy the minimum birth weight was 700 gm and maximum 1900 gm and the mean birth weight was  $1145 \pm 329$  gm. In the group with laser therapy minimum and maximum of post menstrual age for laser therapy was 32 and 42 weeks, respectively. Post natal age for laser therapy was minimally 6 weeks and maximally 12 weeks (Tables 2 and 3).

With stepwise forward logistic regressed three variables including birth weight, duration of oxygen therapy, need of mechanical

**Table 3:** Comparison of means of some variables in the group without retinopathy of prematurity (ROP) or regressed ROP (Group1) and the group of ROP that needed laser therapy (Group 2)

Variables	Groups of ROP	No	Mean $\pm$ SD	P value
<b>Gestational age (weeks)</b>	Group1	180	$31.0 \pm 2.0$	0.002
	Group 2	19	$29.0 \pm 2.3$	
<b>Birth weight (gram)</b>	Group1	180	$1419.2 \pm 316.8$	0.002
	Group 2	19	$1145.8 \pm 329.3$	
<b>Apgar score of first minute</b>	Group1	180	$6.8 \pm 1.8$	0.02
	Group 2	19	$5.8 \pm 1.7$	
<b>Days with mechanical ventilation</b>	Group1	180	$2.2 \pm 5.4$	0.008
	Group 2	19	$9.1 \pm 10.2$	
<b>Days of oxygen therapy</b>	Group1	180	$8.9 \pm 9.3$	0.001
	Group 2	19	$27.5 \pm 19.2$	
<b>Frequency of blood transfusion</b>	Group1	180	$0.7 \pm 1.1$	0.005
	Group 2	19	$1.5 \pm 1.3$	

\* ROP: Retinopathy of prematurity

**Table 4:** Comparison of some variables in the group without retinopathy of prematurity (ROP) or ROP regressed spontaneously (Group 1) and the group of ROP that needed laser therapy (Group 2)

Variable	Group 1 (180)	Group 2 (19)	P-value
<b>P<sub>a</sub> O<sub>2</sub> &lt; 50 mmHg</b>	79 (43.88%)	14 (73.68%)	0.013
<b>P<sub>a</sub> CO<sub>2</sub> &lt; 30mm Hg</b>	115 (63.88%)	16 (84.2%)	0.07
<b>PH &lt; 7.2</b>	42 (23.33%)	5 (26.31%)	0.078
<b>P<sub>a</sub> O<sub>2</sub> &gt; 100mm Hg</b>	120 (66.7%)	17 (89.5%)	0.041
<b>P<sub>a</sub> CO<sub>2</sub> &gt; 60mmHg</b>	23 (12.77%)	6 (31.57%)	0.03
<b>pH &gt; 7.45</b>	56 ( 31.11%)	12 (63.15%)	0.005
<b>Preeclampsia-eclampsia</b>	50 (27.77%)	1 (5.26%)	0.049
<b>Small for gestational age</b>	39 (21.66%)	3 (15.78%)	0.76
<b>Intraventricular hemorrhage</b>	15 (8.33%)	3 (15.78%)	0.38

ventilation, had significant *P*-values. Odd's ratio for duration of oxygen therapy was 1.093 (CI<sub>95%</sub>: 1.055-1.133), for birth weight was 0.997 (CI<sub>95%</sub>: 0.995-0.999) and for need of mechanical ventilation was 4.108 (CI<sub>95%</sub>: 1.014-16.642). We found significant *P*-value by univariate analysis for risk factors like gestational age, birth weight, Apgar of first minute, mean duration of mechanical ventilation, mean duration of oxygen therapy, mean frequencies of blood transfusion, P<sub>a</sub>O<sub>2</sub><50mmHg, P<sub>a</sub>O<sub>2</sub>>100mmHg, P<sub>a</sub>CO<sub>2</sub>>60mm Hg, pH>7.45, for severe ROP that needed laser therapy.

Preeclampsia-eclampsia of mother was associated with lower incidence of severe ROP in our study (Tables 4 and 5).

## Discussion

ROP continues to be an important cause of potentially preventable blindness worldwide<sup>[9]</sup>.

Our study represents a descriptive study evaluating the incidence, risk factors and severity of ROP in Shiraz, Iran. In our study the incidence of ROP with spontaneous regression and ROP that needed laser therapy was 32.6% and 9.5%, respectively. In comparison with other studies we had higher incidence of severe ROP that needed laser therapy, for example Shah et al found at 2005 in Singapore on 564 preterm infants an incidence of 29.2% and the incidence

of ROP that needed surgical treatment was 4.96%<sup>[10]</sup>.

Seiberth et al (2000) on 402 preterm infants from Germany reported an incidence of 36.06% for stage 1 to 5 ROP<sup>[11]</sup>. Karna et al from America reported the incidence of 7.8% for severe ROP (ROP from stage 2 or higher) on 576 preterm infants from 1993 to 2000<sup>[12]</sup>. In study by Yang et al, Taiwan, on 108 preterm infants the incidence of threshold ROP was 7%<sup>[1]</sup>. Another study by Riazzi-Esfahani from Tehran on 150 preterm neonates the incidence of ROP was 6%<sup>[13]</sup>. Higher incidence of ROP in our study can be attributed to admission of more unstable infants in our center as a referral hospital.

This finding is similar to Karkhaneh et al study on 953 premature infants at Farabi ophthalmology tertiary hospital in Tehran from 2003-2007 that reported 22.6% severe ROP needing treatment<sup>[14]</sup>.

Shah et al reported risk factors including: birth weight, gestational age, Apgar in first minute, intraventricular hemorrhage, duration of oxygen therapy and mechanical ventilation for ROP<sup>[10]</sup>. Seiberth et al reported risk factors including: birth weight, gestational age, mechanical ventilation longer than 7 days, blood transfusion and surfactant administration. Preeclampsia-eclampsia were reported with lower incidence of ROP in that study<sup>[11]</sup>.

Karna et al reported low gestational age, mechanical ventilation dependency for longer than 2 weeks, and steroid administration for longer than 2 weeks<sup>[12]</sup> as the risk factors for

ROP. Yang et al saw mechanical ventilation longer than 5 days, periventricular leukomalacia and chronic lung disease risk factors for ROP<sup>[1]</sup>.

## Conclusion

ROP occurs in premature retina. Association of different risk factors with ROP reported by several authors, suggest that ROP is strongly associated with smaller, more immature sick infants. To reduce the incidence of severe ROP premature delivery should be prevented, judicious oxygen therapy and proper management provided at the first weeks of life.

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**Conflict of Interest:** None

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